Inhaled corticosteroids in COPD

The importance of presenting absolute cell numbers when counting cells in biological samples is illustrated by the potentially misleading interpretation of data in the paper by Marco Confalonieri and colleagues. The authors concluded that, in addition to reduced sputum neutrophilia, the number of sputum macrophages increased significantly following treatment with inhaled beclomethasone dipropionate in patients with COPD. However, the observed increase in the proportion of sputum macrophages from 19.6% before treatment to 35.8% following treatment is entirely attributable to the reduced number of sputum neutrophils. From the data presented in the paper, the absolute numbers of different cells in the sputum can be calculated (table 1), revealing that the absolute sputum macrophage count was essentially unchanged following treatment. It is important that the absolute numbers of cells, and not simply their proportions, are presented when measuring differential cell counts in sputum or any other biological sample.

Simon Hart
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Authors’ reply

We would like to thank Dr Hart for his useful comment. We agree that it is important that the absolute numbers of cells are presented when measuring differential cell count in a biological sample. In fact, fig 1 of our paper illustrated the reduction of sputum neutrophils as absolute cell numbers. We thank Dr Hart for the table where the data have been presented as mean absolute cell counts, showing no difference in the absolute number of macrophages after treatment and confirming that the increase in the proportion of sputum macrophages following treatment is attributable to the reduced number of sputum neutrophils. However, the presentation of data as absolute cell numbers did not change the major conclusion of our article that a two month course of treatment with high dose inhaled beclomethasone dipropionate significantly reduces the sputum neutrophil count in patients with clinically stable, smoking related COPD.

Marco Confalonieri
Ospedale Civile, Piacenza, Italy

Antonio Spanevello
Fondazione Mangiagalli, Tradate (VA), Italy

I was very interested to read the article by Confalonieri et al published recently in Thorax. It is interesting that the sputum neutrophil count was reduced after two months of treatment with inhaled beclomethasone with no parallel improvement in spirometric parameters and blood gas data. My group has recently completed a study on the effects of inhaled fluticasone (500 mg twice daily) via the Accuhaler device on 24 patients with severe state bronchiectasis in a double blind, placebo controlled manner. After eight weeks of treatment we also found a significant reduction (p<0.05) in the sputum neutrophil density and the levels of interleukin (IL)-1, IL-8, and leukotriene B4, but no parallel changes in Sao2, or lung function indices. There is little doubt that bronchoectatic inflammation occurs in bronchiectasis, COPD and asthma, and plays an important role in the pathogenesis of these diseases. Although inhaled steroid therapy is undoubtedly effective in asthma, its use in COPD has not shown any clinical benefits from the trials reported to date. Similarly, little is known of the efficacy of inhaled steroid therapy in bronchiectasis despite its anti-inflammatory effects. It is possible that the clinical benefits of inhaled steroid therapy in COPD and bronchiectasis will only be shown by long term studies in large numbers of subjects in view of the more “fixed” damage in these two conditions. The similarity of the findings of Confalonieri et al and my group is exciting and should lead to further research in the use of anti-inflammatory treatment in COPD and bronchiectasis.

Kenneth W Tsang
Division of Respiratory and Critical Care Medicine, University Department of Medicine, University of Hong Kong, Hong Kong SAR, China

We read with interest the effect of inhaled corticosteroids in reducing the neutrophil count in patients with chronic obstructive pulmonary disease (COPD). This highlights the value of sputum induction as a tool in the study of airway inflammation in a diverse range of airway diseases. The authors have concentrated on the effect of beclomethasone dipropionate on neutrophilic inflammation, but we note that in both the control and treatment groups the mean sputum eosinophil count was diыctly related to airway obstruction could also clarify the similarities and differences in distinct airway diseases with fixed obstruction.

Marco Confalonieri
Ospedale Civile, Piacenza, Italy

Antonio Spanevello
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Table 1

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>240</td>
<td>139</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>176</td>
<td>72.3</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>8.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>9.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Macrophages</td>
<td>47.0</td>
<td>19.8</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>2.6</td>
<td>3.2</td>
</tr>
</tbody>
</table>


Authors’ reply

We would like to thank Dr Tsang for his interesting comment. We appreciate his finding of a similar effect of inhaled corticosteroids both on cells and inflammatory mediators in a group of patients with bronchiectasis without any parallel changes in Sao2, or lung function indices. We agree with Dr Tsang on the necessity of long term trials with a sufficient number of subjects to show any beneficial effect of inhaled corticosteroids on inflammatory airway diseases other than asthma. In fact, as mentioned in our paper, Stanescu et al showed that airway obstruction as well as accelerated decline in lung function are associated with increased numbers of neutrophils in the sputum. This suggests that a reduction in airway inflammation (neutrophils) might influence the decline in lung function only over a long period of time. Further research on the effect of corticosteroids on airway inflammation could also clarify the similarities and differences in distinct airway diseases with fixed obstruction.

Marco Confalonieri
Ospedale Civile, Piacenza, Italy

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interpretation of trials of corticosteroid therapy in COPD will remain difficult.

MARC O CONFALONIERI
Ospedale Civile, Piacenza, Italy

ANTONIO SPANEVELLO
Fonazione Mangiato, Triviso (VE), Italy

Coal mining and COPD

Professors Coggion and Newman Taylor correctly state that it is my opinion that the adverse effects of cigarette smoking vary markedly with only around 15–20% of smokers being affected, while the effects of coal mine dust are much more evenly distributed. They find my arguments unconvincing because Fletcher and coworkers’ “semital longitudinal study into the natural history of COPD found that the presence of chronic bronchitis had no independent influence on the decline of the FEV1.”

I yield to none in my admiration for the work of Fletcher and his coworkers, but it needs to be pointed out that the men they selected were “aged 30 to 59 years since young men were chosen deliberately to avoid the effect of other inhaled dusts and cigarette smoke.” While non-smoking men aged 23–35 show either an extended plateau or a period of slow continued growth, at about the age of 35 they start to lose FEV1, due to ageing. In contrast, male smokers show a plateau or a minimal increase between the ages of 23 and 30 but a decline in the FEV1, at the start of the third decade, with the rate being slightly greater than that for non-smokers over the age of 35. In addition, the increase in the FEV1 between the ages of 20 and 30 in smokers is substantially less than that noted in non-smokers. There is a rapid progressive decline in the FEV1 of smokers occurs later, around the age of 40–45 years. The early decline in young persons appears completely reversible and cannot be attributed to emphysema. Moreover, it is known that many young smokers have what is termed a “smoker’s cough” with the production of sputum. In this connection Coggion and Newman Taylor quote two papers, both of which claim to show the early onset of a decline in the FEV1 in coal miners—that is to say, in the first 10 years. None of these early changes would have been apparent in the studies of Fletcher and colleagues.

Coggion and Newman Taylor quote two papers, both of which claim to show the early onset of a decline in the FEV1 in coal miners—that is to say, in the first 10 years. None of these early changes would have been apparent in the studies of Fletcher and colleagues.

AUTHORS’ REPLY We remain unconvinced that bronchitis can explain other than at most a small part of the loss of FEV1 associated with exposure to coal mine dust. If bronchitis had a major influence on airflow, we would have expected it to be apparent in Fletcher’s study. Professor Morgan refers to an early decline in FEV1 in young smokers that is reversible and therefore cannot be attributable to emphysema, and also to a mean decline in FEV1 of 50 ml among older smokers with established chronic airflow obstruction who stop smoking. However, he does not indicate that these effects are restricted to, or even more prominent in, subjects with symptoms of bronchitis. Moreover, the improvement of 50 ml is small in comparison with the deficits of FEV1, associated with coal mine dust, which average more than 225 ml in miners with heavy cumulative exposure. These deficits persist after cessation of exposure and are of similar magnitude in miners with and without symptoms of bronchitis. For these reasons and the others set out in our review, we stand by our conclusion that there is strong evidence that coal mine dust can have a critical influence on health in an important number of people.

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A NEWMAN TAYLOR
Department of Occupation and Environmental Medicine, Imperial School of Medicine at National Heart and Lung Institute, London SW3 6NP, UK

AUTHORS’ REPLY We remain unconvinced that bronchitis can explain other than at most a small part of the loss of FEV1 associated with exposure to coal mine dust. If bronchitis had a major influence on airflow, we would have expected it to be apparent in Fletcher’s study. Professor Morgan refers to an early decline in FEV1 in young smokers that is reversible and therefore cannot be attributable to emphysema, and also to a mean decline in FEV1 of 50 ml among older smokers with established chronic airflow obstruction who stop smoking. However, he does not indicate that these effects are restricted to, or even more prominent in, subjects with symptoms of bronchitis. Moreover, the improvement of 50 ml is small in comparison with the deficits of FEV1, associated with coal mine dust, which average more than 225 ml in miners with heavy cumulative exposure. These deficits persist after cessation of exposure and are of similar magnitude in miners with and without symptoms of bronchitis. For these reasons and the others set out in our review, we stand by our conclusion that there is strong evidence that coal mine dust can have a critical influence on health in an important number of people.
BOOK REVIEW


This is a comprehensive and technically detailed book which will, I think, be of value to laboratory workers and perhaps some interested clinicians who wish to have authoritative accounts of research into the application of oncological biology to the early detection and, to a lesser extent, the prevention of lung cancer.

In 1996 the International Association for the Study of Lung Cancer (IASLC) sponsored two workshops on lung cancer prevention, the first focusing on clinical studies and the second—the subject of this book—focusing on basic laboratory work which was held in Nancy in France. This volume consists of 30 separate papers delivered at the workshop and edited for publication.

Although the title of the book emphasises prevention, to my mind the bulk of it essentially looks at laboratory investigations of risk factors and changes in the bronchial epithelium and the early evolution of tumours which might, with luck, be translated into strategies for early detection of lung cancer rather than its prevention. Of course, this is a hugely important problem; 90% of lung cancers are caused by tobacco inhalation but it is unknown why only about 15% of smokers are susceptible to malignant change. Sadly, it is widely recognised that primary prevention—a largely a matter of social policy and public pressure—is failing even in the developed world and, with the unopposed expansion of tobacco marketing in the third world, from a global perspective the lung cancer epidemic is set to continue for the foreseeable future and to be concentrated in communities where the prospects of using elaborate techniques for early detection or prevention are bleak.

It is also well recognised that the lung cancer screening programmes using presently available techniques such as plain radiography and sputum cytology are not cost effective (unlike cancer of the cervix and cancer of the breast). This situation may change in some communities and there is now interest in portable spiral computed tomographic scanning, possibly coupled with the examination of chromosomal abnormalities in sputum in high risk individuals, which may to a certain extent bridge the gap between what is presently achievable and what the articles in this book hold out as tantalising promises.

The scope of laboratory work described here is wide. Amongst others, those that came to my attention included genetic susceptibility, chemoprevention, pre-malignant changes, inhibitory growth factors, and fluoroscopic bronchoscopy. For genetic susceptibility, I learnt that polymorphisms of a regulatory gene might determine the inducibility of two forms of cytochrome p450 by tobacco smoke which leads to a variable ability of tobacco smoke to convert pro-carcinogens into carcinogenic metabolites. Other polymorphisms may add to these risks. Sadly, the theoretical promise of primary chemoprevention using substances thought to inhibit carcinogenesis (β-carotenes and α-tocopherol) do not seem to have been borne out in clinical trials (Pastorino and Sasco).

Running throughout many chapters is the concept that there is a cascade of pre-malignant changes in bronchial epithelium involving genetic damage and which, if detected at an early stage, might allow more effective treatment. However, this hypothesis—although promising for squamous carcinoma—seems to be supported less strongly with respect to adenocarcinoma and small cell carcinoma. The particular value of studying these early genetic abnormalities is, it seems to me, that they may be reflected in sputum samples, and with a high proportion of carcinomas now presenting in the UK in ex-smokers as opposed to present smokers, in whom of course prevention is inappropriate, early treatment might be possible. A chapter discussing fluorescence bronchoscopy (Lam McAulay) shows that early lesions can be identified, but this particular volume does not include data showing that early detection in this way yields better survival figures. Not surprisingly, because of the possibility of improved therapy, there are papers on inhibitory growth factors such as metalloproteinases (Vignaud et al) and neuropeptides (Seckel and Rozengurt) in relation to small cell lung cancer which demonstrate how powerful synthetic inhibitors of these substances might be.

I came away from reading this book with a strong impression of the ingenuity and the variety of potential anti-cancer strategies that are being studied. It would be far too optimisitic to suppose that the subjects of all of these 30 chapters will in due course be shown to be fundamental to a novel and important way of either detecting lung cancer earlier, preventing it, or inhibiting it. But only a pessimist would suppose that nowhere in this comprehensive book is there a discussion of an approach which will eventually be found to be clinically useful and justify the huge research effort so carefully described in these pages.—MM

NOTICES

Fleischner Society

The Fleischner Society’s 29th Annual Conference on Chest Disease will be held on 18–21 April 1999 at the Loews Ventana Canyon Resort, Tucson, Arizona, USA. For further information contact Lynne Tiras or Pam Waslawski, International Meeting Managers Inc., 4550 Post Oak Place, Suite 342, Houston, Texas 77027, USA. Telephone +1 713 965 0566; Fax +1 713 960 0488.

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the Dr H M (Bill) Foreman Memorial Fund invite applications for grants related to study in respiratory disease and allied fields. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study respiratory disease and also for support for clinical research abroad. Intending applicants should write for further details to Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2XX, UK.

CORRECTION

Long term treatment with salbutamol and salmeterol

In the paper entitled “Asthma control during long term treatment with regular inhaled salbutamol and salmeterol” by D R Taylor which appeared in the September 1998 issue of Thorax on pp 744–52, Figure 2 on page 749 was incorrect. A correct version of Figure 2 appears below.

Figure 2 Kaplan-Meier plot showing the proportion of patients who remained free of exacerbations during each treatment period (days). This was significantly greater for salmeterol than for salbutamol compared with placebo in subjects for whom paired comparisons were possible (α = 0.146; p = 0.008).

Inhaled corticosteroids in COPD

SIMON HART

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